sertation Fellow (1978–1979); L.N. was an American Oil Fellow (1977–1978). We thank C. M. Wong for a sample of **33b** and R. B. Garland for samples of **34a** and **34b**. The 300-MHz FT NMR spectra were obtained at The Ohio State University Chemical Instrument Center (funded in part by NSF Grant CHE-7910019) with the help of Dr. C. E. Cottrell and Mr. Gary Larson.

Registry No. **1**, 17644-94-9; **2**, 6383-11-5; **3b**, 79190-97-9; **3c**, 79190-98-0; **4b**, 60316-51-0; **6**, 6383-64-8; **7**, 71192-84-2; **8**, 6119-74-0; **9**, 79190-99-1; **10a**, 71192-85-3; **10b**, 33628-86-3; **11a**, 79191-00-7; **11b**, 71192-92-2; **12a**, 79191-01-8; **12b**, 79191-02-9; **13**, 68216-66-0; **14**, 71192-94-4; **15a**, 71192-87-5; **15b**, 71192-86-4; **15c**, 79191-03-0; **15d**, 79191-04-1; **16**, 79191-05-2; **17a**, 79191-06-3; **17b**, 71192-88-6; **18a**, 71192-95-5; **18a** β-keto sulfoxide, 79191-07-4; **18b**, 71192-89-7; **18b** β-keto-sulfoxide, 79191-08-5; **19a**, 71192-91-1; **19b**, 71192-90-0; **21**, 79191-09-6; **22**, 62416-22-2; **23**, 79191-10-9; **28a**, 78752-32-6; **28b**, 78752-34-8; **29a**, 78752-38-2; **29b**, 79191-11-0; **30a**, 78752-39-3; **30b**, 79191-12-1; **32a**, 33676-07-2; **32b**, 33628-88-5; **33a**, 33632-97-2; **33b**, 79253-99-9; **34a**, 58924-49-5; **34b**, 65877-42-1; **35**, 79254-00-5; 7-bromo-5,8-dimethoxy-2-hydroxy-2-(carbomethoxy)tetralin, 79191-13-2; 7-bromo-5,8-dimethoxy-2-(carbomethoxy)tetralin, 79191-14-3; 7-bromo-5,8-dimethoxy-2-hydroxy-2-acetyltetralin, 79191-15-4; 7-bromo-5,8-dimethoxy-2-hydroxy-2-acetyltetralin ethylene glycol ketal, 79191-16-5; (±)-daunomycinone, 59367-19-0.

Diels–Alder Adducts of 1-Benzenesulfonylindole-2-acrylates and 1-(Alkoxycarbonyl)-1,2-dihydropyridines. Intermediates for Synthesis of Iboga Alkaloid Analogues

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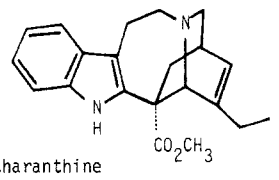
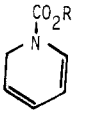
Diels–Alder reactions between methyl 1-benzenesulfonylindole-2-acrylate and several 1-(alkoxycarbonyl)-1,2-dihydropyridines give protected methyl 7-(2-indolyl)-2-azabicyclo[2.2.2]octene-7-carboxylates which serve as intermediates for the synthesis of analogues of the iboga alkaloids. Methods for deprotection of both the carbamate nitrogen and indole nitrogen are reported. The 7-(2-indolyl)-2-azabicyclo[2.2.2]octene-7-carboxylates show a tendency to undergo fragmentation of the C-1,C-7 bond of the 2-azabicyclo[2.2.2]octene ring, probably by retro-Mannich reactions. Several 6-nor-20-deethyl analogues of catharanthine have been prepared from intermediates derived from the deprotected Diels–Alder adducts.

Both biogenetic proposals[1] and retrosynthetic analysis bring the Diels–Alder reaction to the fore in considerations of routes for synthesis of members of the iboga group of indole alkaloids, such as catharanthine. Indeed, the reaction has played a prominent role in synthetic studies in this area.[2-4] We recently demonstrated that esters of 1-benzenesulfonylindole-2-acrylic acid reacted with both 1-(ethoxycarbonyl)- and 1-(methoxycarbonyl)-1,2-dihydropyridine to give Diels–Alder adducts regiospecifically in good yield and with stereoselectivity (~10:1) suitable for elaboration to the iboga skeleton. These adducts proved to be satisfactory intermediates for the synthesis of deethylcatharanthine.[3] In that work the carbamate group derived from the dihydropyridine precursor was removed by vigorous alkaline hydrolysis. With the goal of increasing the synthetic versatility of this type of adduct, we have examined several other 1-substituted dihydropyridines and report here on the Diels–Alder reactions with methyl 1-benzenesulfonylindole-2-acrylate and relevant chemical reactions of the adducts. The (alkoxycarbonyl)-1,2-dihydropyridines which we examined are shown as structures **1a–c** and constitute a series of groups



Catharanthine



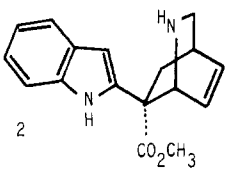
1a R = $C(CH_3)_3$

b R = CH_2Ph

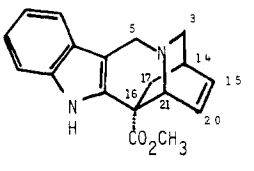
c R = CH_2CCl_3

d R = C_6H_5

which are subject to nonhydrolytic cleavage. Compound **2** was considered to be a particularly desirable target as an intermediate since it offered the potential reactivity of the indole 3-position and the amine nitrogen as sites for reactions to close the tryptamine bridge of the iboga system or, with one-carbon reagents, the 6-nor skeleton. This structural family has become of interest as the result of encouraging biological results obtained with 6-noranhydrovinblastine.[5]



2



20-desethyl-6-norcatharanthine

(1) A. I. Scott, *Acc. Chem. Res.*, **3**, 151 (1970); J. P. Kutney, J. F. Beck, C. Ehret, G. Poulton, R. S. Sood, and N. D. Westcott, *Bioorg. Chem.*, **1**, 194 (1971); A. I. Scott, *ibid.*, **3**, 398 (1974).

(2) G. Büchi, P. Kulsa, K. Ogasawara, and R. L. Rosati, *J. Am. Chem. Soc.*, **92**, 999 (1970); G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *ibid.*, **88**, 3099 (1966).

(3) R. J. Sundberg and J. D. Bloom, *J. Org. Chem.*, **45**, 3382 (1980).

(4) C. Marazano, J.-L. Fourrey, and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 37 (1981).

(5) P. Potier, D. Guénard, and F. Zavala, *C. R. Seances Soc. Biol. Ses Fil.*, **173**, 414 (1979); P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Org. Chem.*, **44**, 3765 (1979); R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *Tetrahedron*, **36**, 3053 (1980).

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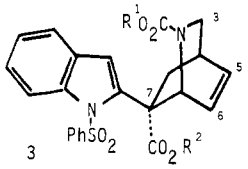
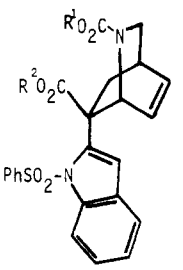
We were not able to prepare **1a** directly from such reagents as 2-[[(*tert*-butoxycarbonyl)oxy]imino]-2-phenylacetonitrile (BocON) or di-*tert*-butyl dicarbonate and pyridine under the reductive conditions used for methyl or ethyl chloroformate.[6] Substantial amounts of the acylating reagents were recovered, suggesting that little acylation of pyridine occurred with these reagents at the low temperature used. A convenient exchange route was developed, however. Phenyl chloroformate reacted with pyridine and sodium borohydride to give the nicely crystalline dihydropyridine **1d**, which in turn was converted by 1.2 equiv of potassium *tert*-butoxide to a 4:1 mixture of **1a** and the corresponding 1,4 isomer. When 2.8 equiv of potassium *tert*-butoxide was used, the product was predominantly the 1,4 isomer. This isomer is undoubtedly formed by base-catalyzed isomerization of **1a**.[7]

The Diels–Alder reaction of **1a** was carried out with methyl 1-benzenesulfonylindole-2-acrylate by heating at 100 °C for 3–5 days. Unreacted excess dihydropyridine could be removed by distillation and typically had a composition of two parts 1,2 isomer and one part 1,4 isomer at the end of the reaction. The adduct obtained in 65% yield after chromatography proved to be a 1:1 mixture of stereoisomers **3a** and **4a**. Evidently the bulky *tert*-butyl



3



4

	R^1	R^2
a	$(CH_3)_3C$	CH_3
b	$PhCH_2C$	CH_3
c	Cl_3CCH_2	C_2H_5
d	Cl_3CCH_2	CH_3
e	CH_3	CH_3
f	C_2H_5	C_2H_5

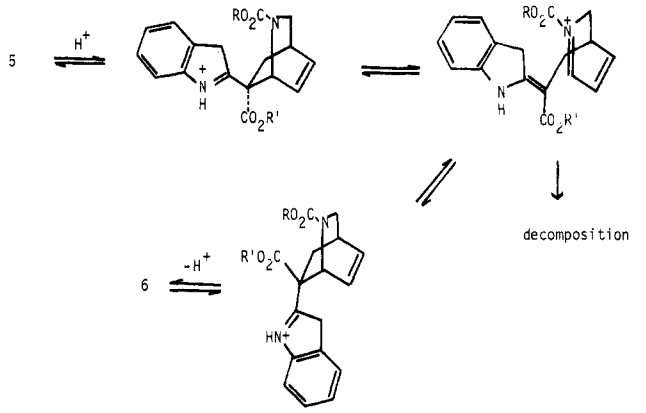
group creates sufficient steric interference with the indole ring to cause the loss of stereoselectivity, relative to the ethoxycarbonyl or methoxycarbonyl compounds. These two isomers were virtually indistinguishable by chromatographic methods, but the complexity of the NMR spectrum argued for the existence of a mixture of stereoisomers. Selective crystallization conditions, as described in the Experimental Section, provided pure samples of **3a** and **4a** and confirmed the interpretation of the NMR data. The most characteristic difference in the spectra is the appearance of the indole 3-H proton at 6.63 ppm in the **4** (endo) isomer series. This is substantially upfield of the corresponding signal in the exo isomer and is attributed to shielding by the carbon–carbon double bond.

1-(Benzyloxycarbonyl)-1,2-dihydropyridine (**1b**) does not appear to have been previously reported, but the synthesis proceeded normally under Fowler's conditions.[6] The Diels–Alder reaction also was similar to those observed with carbomethoxy and carboethoxy compounds. A single stereoisomer, **3b**, was isolated in 73% yield as crystalline material and proved to have NMR absorptions characteristic of the desired exo stereochemistry.

1-[(2,2,2-Trichloroethoxy)carbonyl]-1,2-dihydropyridine (**1c**) has previously been reported by Mariano and coworkers[8] and was prepared in the standard way. The

(6) F. W. Fowler, *J. Org. Chem.*, **37**, 1321 (1972).
(7) R. R. Schmidt and G. Berger, *Chem. Ber.*, **109**, 2936 (1976).

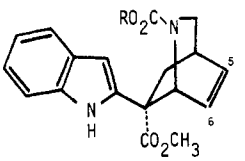
Scheme I

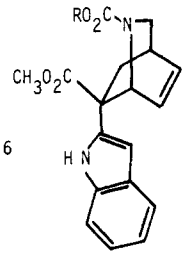


Diels–Alder reactions with both ethyl and methyl 1-benzenesulfonylindole-2-acrylate proceeded in lower yield than for the other systems. Only a single stereoisomer was isolated after chromatography in each case, through any of several minor uncharacterized components of the mixture could have been the endo stereoisomers **4c** and **4d**. The yields of crystalline ethyl and methyl esters **3c** and **3d**, respectively, were 31% and 13%.

The carbamates **3a–c** were correlated with the previously characterized[3] **3e** by exchanging the carbamate substituent for methyl. In the case of the *tert*-butoxy carbamate **3a**, stirring for 6–12 h with *p*-toluenesulfonic acid in acetonitrile cleaved the *tert*-butoxy group, and reaction with methyl chloroformate then gave **3e**. Reaction of **3b** with trimethylsilyl iodide[9] in methylene chloride for 2 h at 0–20 °C followed by reaction with methyl chloroformate similarly gave **3e**. Finally, **3d** was converted to **3e** by zinc–acetic acid reductive cleavage, followed by reaction with methyl chloroformate. These transformations verified the assignments of stereochemistry which had been made on the basis of NMR comparison with the previously characterized methoxycarbonyl and ethoxycarbonyl adducts.

The objective then became the combining of the carbamate deprotection methodologies, which had proceeded satisfactorily for **3a**, **3b**, and **3d**, with methodology for deprotection of the indole group to give **2**. The *N*-benzenesulfonyl group can often be removed from the indole ring rapidly and cleanly by reaction with potassium *tert*-butoxide in tetrahydrofuran.[10] This process was applied successfully to **3a** to give **5a** in 57% yield. Ap-



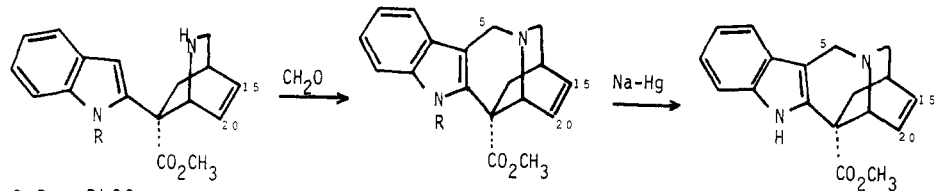


6

5a, R = $(CH_3)_3C$
b, R = $PhCH_2C$
e, R = CH_3
f, R = CH_3CH_2
g, R = CH_3CH_2, ethyl ester
7, R = CH_3CH_2, ethyl ester, 5,6-dihydro

(8) P. S. Mariano, D. Dunaway-Mariano, P. L. Husemann, and R. L. Beamer, *Tetrahedron Lett.*, 4299 (1977).
(9) M. E. Jung and M. A. Lyster, *J. Chem. Soc., Chem. Commun.*, 315 (1978).
(10) The utility of potassium *tert*-butoxide in tetrahydrofuran for removal of benzenesulfonyl groups from the indole ring was kindly communicated to us by Richard Besselievre, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France, 1978.

Scheme II

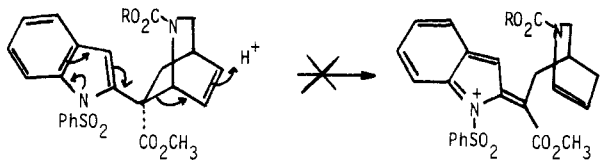


8 R = $PhSO_2$
12 R = H, 15,16-dihydro
14 R = $PhSO_2$, 15,20-dihydro

9 R = $PhSO_2$
15 R = $PhSO_2$, 15,20-dihydro
17 R = $PhSO_2$, C-5 CH_3-

10
13 15,20-dihydro

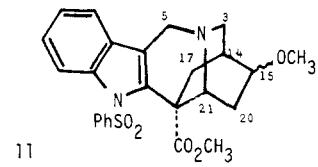
plication of the *p*-toluenesulfonic acid–acetonitrile conditions, which successfully cleaved the *tert*-butoxycarbonyl group from **3a**, led to an unexpected result. Over a period of about 20 min, i.e., much faster than *tert*-butoxy cleavage, **5a** was partially converted to the stereoisomer **6a**. More slowly, but still more rapidly than the deprotection occurred, the stereoisomeric mixture decomposed to intractable materials (Scheme I). The experiment was also conducted by starting with **6a**, in which case **5a** appeared in the mixture, followed by the same decomposition. This behavior was also observed with the *N*-carboethoxy adducts **5f** and **6f**. Rapid interconversion of the stereoisomers to a roughly 1:1 mixture followed by decomposition was observed. The dihydro compound **7f** was substantially more stable to these acidic conditions. Under conditions of increased reaction time and acid concentration corresponding to >100-fold increase in reactivity, compound **7f** underwent negligible change. We consider the stereoequilibration and decomposition to be the result of a fragmentation initiated by 3-protonation of the indole ring. The effect of the conjugating double bond is very substantial, judging from the relative stability of the dihydro compound. The bond fragmentation corresponds to a well-known process in the iboga alkaloid series,[11] but the facility with which it occurs was surprising. This is probably due to the fact that, in contrast to the alkaloids where the nitrogen is usually a tertiary amine and therefore the primary site of protonation, in these carbamates the nitrogen is not competing strongly with the indole 3-position as a site of protonation. An alternative mechanism involving initial protonation of the double bond followed by indole ring participation seems less satisfactory since



it is unlikely that this fragmentation could be followed by recyclization without a skeletal rearrangement. The facility of the acid-catalyzed epimerization and decomposition of **5a** stymied this particular approach to **2**.

Adduct **3a** nevertheless provided access to the 6-nor analogue of deethylcatharanthine. After removal of the *tert*-butoxy group by *p*-toluenesulfonic acid in acetonitrile, reaction with formaldehyde gave the cyclized tertiary amine **9**, the structure of which was confirmed by high-field NMR data given in Table I. The aliphatic region is completely resolved in benzene-d_6, and both in benzene-d_6 and in $CDCl_3$ there is a prominent AB quartet at δ 3.94 and 4.31 ($CDCl_3$) due to the C-5 methylene group.

The preferred conditions for the formaldehyde cyclization involved addition of an anhydrous solution of formaldehyde in tetrahydrofuran to the acidic acetonitrile solution resulting from cleavage of the *tert*-butoxy group. The yield of **9** was 60–70% under these conditions. The formaldehyde solution was freshly prepared from gaseous formaldehyde obtained by pyrolysis of paraformaldehyde. Alternatively, the product was obtained in up to 55% yield by stirring the solution from the deprotection step with solid paraformaldehyde, but this reaction was not completely predictable. When a methanolic solution of formalin was used as the formaldehyde source, addition of methanol to the C-15,C-20 double bond occurred to give **11**. Interestingly, compound **9** did not add methanol



11

under comparable conditions, so the methanol addition must take place prior to cyclization. The most likely mechanism for the methanol addition is via a reversible Mannich reaction of secondary amine **8** to the corresponding α,β-unsaturated iminium ion. This mechanism would predict that the methoxy group would be introduced at the C-15 position. The structure of **11** is consistent with the high-field NMR spectrum as reported in Table I. The disappearance of the C-15,C-20 double bond and the appearance of a new methoxyl peak are evident. Assignment of three downfield peaks, two of which are partially obscured by other peaks, was aided by decoupling experiments. A doublet of triplets at 3.54 ppm is assigned to one of the C-3 methylene hydrogens. The geminal coupling constant of 8 Hz agrees with that observed for the analogous pair of protons in norcatharanthine.[12] Decoupling locates the other C-3 proton at 1.95 ppm. The C-14 proton is recognizable as the only high-field proton lacking a geminal coupling. It is coupled to a multiplet (partially obscured) at 3.45 ppm which is assigned to the C-15 proton. This peak is, in turn, coupled to the doublet of doublets at 2.35 ppm which must be one of the C-20 methylene group protons. Decoupling locates the second C-20 proton at 2.03 ppm. The C-21 bridgehead proton appears at 3.05 ppm and is coupled to the 2.35-ppm doublet of doublets

(11) Examples include the following. The acid-catalyzed (refluxing acetic acid) rearrangement of catharanthine to pseudocatharanthine: R. T. Brown, J. S. Hill, G. F. Smith, K. S. J. Stapleford, J. Poisson, M. Muquet, and N. Kunesch, *J. Chem. Soc. D*, 1475 (1969); R. T. Brown, J. S. Hill, G. F. Smith, and K. S. J. Stapleford, *Tetrahedron*, **27**, 5217 (1971); M. Gorman, N. Neuss, and N. J. Cone, *J. Am. Chem. Soc.*, **87**, 93 (1965). The reductive cleavage of catharanthine to cleavamine derivatives: N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *J. Am. Chem. Soc.*, **86**, 1440 (1964); J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, and V. R. Nelson, *J. Am. Chem. Soc.*, **92**, 1704 (1970).

(12) R. Z. Andriamialisoa, N. Langlois, Y. Langlois, P. Potier, and P. Bladon, *Can. J. Chem.*, **57**, 2572 (1979).

Table I. Proton NMR Data

compd	aromatic	H-3	H-5	H-14	H-15	H-17	H-20	H-21	C-16 CO_2CH_3	other
					(A) High-Field Data[a,e]					
9	7.95 (m), 7.82 (d), 7.08 (m), 7.03 (m), 6.76 (t), 6.71 (t)	2.75 (dt, J = 9, 2, 2), 1.85 (d, J = 9)	4.03, 3.58 (AB, J = 16)	2.10 (m)	6.35 (td, J = 6, 1)	2.92 (dt, J = 14, 2, 2), 1.75 (dd, J = 14, 3)	6.27 (t, J = 6)	3.73 (d, J = 6)	3.31 (s)	
9[b]	7.79 (d), 7.73 (m), 7.56 (t), 7.45 (t), 7.41 (m), 7.25 (m)	3.0 (dt, J = 9, 2, 2), 2.38 (d, J = 9)	4.31, 3.95 (AB, J = 16)	2.67 (m)	6.45 (td, J = 6, 1)	2.67 (dt, J = 14, 2, 2), 1.80 (dd, J = 14, 3)	6.57 (t, J = 6)	3.69 (d, J = 6)	3.50 (s)	
11	7.95 (m), 7.72 (d), 7.1–7.5[c] (m), 7.04 (m), 6.76 (t), 6.69 (t)	3.54 (dt, J = 9, 2, 2), 1.95 (d, J = 9)	4.00, 3.46 (AB, J = 16)	1.70 (m)	3.45[c] (m)	2.90 (dt, J = 14, 2, 2), 1.95[c]	2.36 (dt, J = 14, 9), 2.03 (dt, J = 14, 2, 2)	3.07[c] (m)	3.27 (s)	3.07 (s, C-15 OCH_3)
15	7.95 (m), 7.75 (d), 7.08 (m), 7.03 (m), 6.75 (t), 6.68 (t)	3.10 (dt, J = 9, 2, 2), 1.9 (d, J = 9)	3.99, 3.49 (AB, J = 16)	1.38 (m)	1.4–1.6 (m)	3.0[c] (m)	2.05 (m), 1.4–1.6 (m)	3.00[c] (m)	3.30 (s)	
17	7.95 (m), 7.83 (d), 7.38 (m), 7.04 (m), 6.72 (m)	2.46 (dt, J = 9, 2, 2), 2.11 (d, J = 9)	4.27 (q, J = 7)	2.18 (m)	6.39 (td, J = 6, 1)	2.95 (dt, J = 14, 2, 2), 1.87 (dd, J = 14, 3)	6.31 (t, J = 6)	3.75 (d, J = 6)	3.32 (s)	1.41 (d, C-5 CH_3, J = 7)

(B) 90-MHz Data[d,e]

3a	7.0–7.7 (m), 6.3–6.7 (overlapping t), 5.3 (d), 5.2 (d), 3.40 (s), 2.8 (m), 1.95 (d), 1.4 (s)
3b	7.0–7.8 (m), 6.3–6.7 (overlapping t), 5.5 (d), 5.2 (d), 3.6 (s), 2.9–3.3 (m), 2.1 (d)
3c	7.0–7.8 (m), 6.3–6.7 (overlapping t), 5.4 (d), 4.9, 4.5 (AB d), 4.1 (overlapping q), 2.8–3.3 (m), 2.1–2.3 (m), 1.2 (t)
3d	7.0–7.8 (m), 6.3–6.7 (overlapping t), 5.4 (d), 4.9, 4.5 (AB d), 3.5 (s), 2.8–3.2 (m), 2.0–2.2 (m)
3e	7.0–7.8 (m), 6.3–6.7 (overlapping t), 5.4 (d), 3.62 (s), 3.55 (s), 2.8–3.1 (m), 2.0 (d)
4a	7.0–7.7 (m), 6.6 (s), 6.4 (t), 6.2 (t), 5.4 (d), 5.3 (d), 3.5 (s), 3.4 (m), 2.6–3.3 (m), 1.8 (m), 1.4 (s)
5a	9.7 (br s), 7.0–7.6 (m), 6.5 (m), 5.6 (m), 3.55 (s), 2.7–3.2 (m), 2.1 (br d), 1.3 (s)
5b	9.4 (br s), 7.0–7.6 (m), 6.5 (m), 5.6 (m), 5.1 (s), 3.55 (s), 2.8–3.3 (m), 2.1 (br d)
8	7.0–7.8 (m), 6.2–6.6 (overlapping t), 4.2 (d), 3.56 (s), 1.7–3.0 (m)
9	7.0–7.8 (m), 6.5 (m), 4.3, 3.9 (AB d), 3.45 (d), 3.4 (s), 2.95 (dt), 2.6 (m), 2.3 (d), 1.8 (dd)
10	8.5 (s), 7.0–7.5 (m), 6.3–6.7 (overlapping t), 4.25, 3.85 (AB d), 3.70 (s), 2.9 (dt), 2.5 (m), 2.4 (d), 1.7–2.0 (m)
11	7.1–7.8 (m), 4.20, 3.70 (AB d), 3.45 (s), 3.32 (s), 2.95 (m), 2.65 (d), 2.30 (m), 1.7–2.1 (m)
12	9.7 (s), 7.1–7.7 (m), 6.45 (s), 3.75 (s), 3.40 (m), 2.8–3.0 (m), 1.6–2.1 (m)
13	8.25 (s), 7.0–7.5 (m), 4.20, 3.85 (AB d), 3.71 (s), 3.15 (m), 2.5 (d), 2.3 (dd), 1.5–1.9 (m)
14	7.0–7.8 (m), 6.78 (s), 3.56 (s), 3.4 (m), 3.2 (t), 2.85 (br d), 3.65 (dt), 2.1 (m), 1.7–2.0 (m)
15	7.0–7.8 (m), 4.15, 3.55 (AB d), 3.45 (s), 3.15 (dt), 2.7–2.9 (m), 2.40 (d), 1.5–1.9 (m)
16	7.0–7.8 (m), 6.45 (overlapping t), 5.4 (d), 5.4 (s), 4.05 (overlapping q), 2.9–3.2 (m), 2.1 (d), 1.1 (s)
17	7.0–7.8 (m), 6.3–6.6 (m), 4.4 (q), 3.6 (m), 3.5 (s), 2.6 (m), 1.6 (d)

[a] In benzene-d_6 at 360 MHz unless otherwise noted. Alkaloid numbering is used. [b] In $CDCl_3$ at 470 MHz. [c] Partially obscured by solvent or overlapping peak. [d] In $CDCl_3$. [e] The chemical shifts are given in δ values, and the J values are given in hertz.

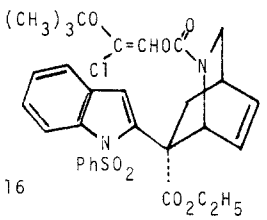
as expected. The remaining peaks at 2.90 (J = 14 Hz) and 1.93 ppm (partially obscured) can be assigned to the C-17 methylene hydrogens.

Attempts to remove the benzenesulfonyl group from **9** failed on using the potassium *tert*-butoxide–tetrahydrofuran method. However, the use of sodium amalgam in methanol in the presence of excess disodium hydrogen phosphate as buffer[13] proceeded smoothly to give **10**, the 6-nor analogue of 20-deethylcatharanthine.

Compound **5b** was readily obtained from **3b** by reaction with potassium *tert*-butoxide in tetrahydrofuran. Two methods for deprotection of **5b** were then examined. Debenzylation with palladium black in methanol by using formic acid[14a] or cyclohexadiene[14b] as the hydrogen source followed by reaction with formaldehyde gave compound **13**, the dihydro analogue of **10**, via the amine **12**. Attempted debenzylation of **5b** with trimethylsilyl iodide rapidly gave an isomeric substance which retained the benzyloxy group but had clearly undergone other significant structural changes on the basis of the NMR spectrum. This material was not investigated in detail, but it appears likely that the unprotected indole ring in **5b** is reacting with trimethylsilyl iodide in preference to the carbamate group.

As mentioned earlier, the benzenesulfonyl derivative **3b** can be debenzylated with trimethylsilyl iodide without interference from the indole ring or reduction of the double bond. Amine **8** prepared in this way could also be cyclized with formaldehyde to give **9**. Debenzylation of **3b** with Pd black and formic acid or cyclohexadiene was accompanied by reduction of the double bond. Formaldehyde cyclization gave **15** via amine **14**. Compound **15** was readily converted to **13** by using sodium amalgam to remove the benzenesulfonyl group.

Use of *tert*-butoxide ion to remove the benzenesulfonyl group from **3c** led to concomitant exchange of the *tert*-butoxy group for trichlorethyl at the carbamate group, giving **5a** in 80% yield. The ethyl ester **3d** behaved similarly. It was possible by TLC and interruption of the exchange process to detect and isolate an intermediate substance, **16**. The elemental composition of **16** corresponded to elimination of two molecules of HCl and addition of one molecule of *tert*-butyl alcohol. The NMR shows a vinyl proton signal at 5.40 ppm. Any of the four possible isomers at the trisubstituted vinyl ester group are mechanistically conceivable, and NMR additivity rules[15] fail to predict a value in agreement with that observed, probably because of anisotropic shielding by either the aromatic ring or the bicyclic double bond. Since amine **8** was readily available from **3d** by reductive removal of the (trichloroethoxy)carbonyl group with zinc, a third route to **9** and **10** from **3d** is also available, although this particular transformation was not carried out.



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The cyclization of **8** by other carbonyl compounds was examined briefly. Acetaldehyde gave a noncrystalline cyclization product **17** which was structurally characterized by its 360-MHz NMR spectrum which indicated that a single stereoisomer (unassigned) was formed. In contrast, when the amine **12** was treated with acetaldehyde, the cyclization product showed two pairs of CH_3 doublets near 1.5 ppm, indicating formation of both possible stereoisomers. These materials were not separable by chromatography and were not fully characterized. Methyl pyruvate did not give a cyclic product from **8** under the conditions of the reaction with acetaldehyde.

In summary, although amine **2** has remained elusive, the benzenesulfonyl protected analogue **8** is easily available from adducts **3a**, **3b**, or **3d**. The dihydro derivative **14** can also be prepared easily from **3b**. These compounds have been used to synthesize representatives of the 20-deethyl-6-norcatharanthine group. The 7-indolyl-2-azabicyclooctene ring contained in this group of intermediates has exhibited a proclivity for fragmentation, reversible or otherwise, via a retro-Mannich reaction. Observation of reactions which apparently proceed via the retro-Mannich process serve to indicate the limits which must be respected in order to maintain the integrity of the bicyclic ring.

Experimental Section

1-(Phenoxycarbonyl)-1,2-dihydropyridine (1d). Pyridine (2.0 g, 0.025 mol), $NaBH_4$ (1.05 g, 0.028 mol), and absolute ethanol (10 mL) were stirred together at −78 °C, and over 1 h freshly distilled phenyl chloroformate (4.0 g, 0.025 mol) was added, with the solution temperature kept below −70 °C. The mixture was stirred 2 h at −78 °C, poured into ice–water, and extracted with ether. After the extract was dried over magnesium sulfate, evaporation of the ether gave the product which was recrystallized from ethanol (51% yield; mp 65–67 °C).

1-(*tert*-Butoxycarbonyl)-1,2-dihydropyridine (1a) and 1-(*tert*-Butoxycarbonyl)-1,4-dihydropyridine. (A) 1.2 Equiv of Potassium *tert*-Butoxide. A solution of potassium *tert*-butoxide (0.91 g, 8.2 mmol) in anhydrous THF (25 mL) was added slowly to a solution of 1-(phenoxycarbonyl)-1,2-dihydropyridine (1.4 g, 6.8 mmol) in anhydrous THF (25 mL). The solution was stirred for 1 h at room temperature, poured into water, and extracted with ether. The ether layer was washed several times with 2% sodium hydroxide, dried, and evaporated to give 1.0 g (80%) of material found by NMR to be a 4:1 mixture of the 1,2- and 1,4-dihydro isomers.

(B) 2.8 Equiv of Potassium *tert*-Butoxide. The experiment was carried out similarly but with the higher ratio of potassium *tert*-butoxide. The recovered material (80%) was >90% 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine as determined by NMR.

1-(Benzyloxycarbonyl)-1,2-dihydropyridine (1b). A solution of pyridine (4.0 g, 0.050 mol) and $NaBH_4$ (2.0 g, 0.026 mol) in 20 mL of absolute ethanol was treated with benzyl chloroformate (8.5 g, 0.050 mol) over about 1 h followed by stirring for 1.5 h at −78 °C. The mixture was added to ice–water and extracted with ether, and the extract was washed with 3% hydrochloric acid and 3% sodium hydroxide solutions. After the extract was dried and evaporated, 8.0 g of dihydropyridine (74%) showing the expected NMR features was obtained.

[(2,2,2-Trichloroethoxy)carbonyl]-1,2-dihydropyridine (1c). The general conditions, as described by Fowler,[6] gave **1c** in 60% yield.

Diels–Alder Reactions. (A) Methyl 1-Benzenesulfonylindole-2-acrylate and 1a. A sample of **1a** containing 20% of the 1,4 isomer (2.4 g, 13.3 mmol) was heated neat with the acrylate (0.73 g) under nitrogen at 100 °C for 5 days. Excess dihydropyridine was removed at ~100–110 °C (~1 mm), and the residual oil was purified by chromatography on silica gel to give **3a** and **4a** as a foam (0.74 g, 65%). Selective crystallization of the isomers occurred after refrigeration of a concentrated ether solution of the mixture. The stereoisomer **3a** crystallized as well-formed,

(13) B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, *Tetrahedron Lett.*, 3477 (1976).
(14) (a) B. El Amin, G. M. Anatharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.*, **44**, 3442 (1979); (b) A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *ibid.*, **43**, 4194 (1978).
(15) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969).

hard crystals whereas **4a** was a flocculent material. The flocculent material could be removed by decantation with the solvent. Separate recrystallization of the two fractions gave the pure stereoisomers.

3a, mp 179–181 °C (after recrystallization from chloroform–hexane). Anal. Calcd for $C_{28}H_{30}N_2O_6S$: C, 64.34; H, 5.80; N, 5.36. Found: C, 64.65; H, 6.05; N, 5.20.

4a, mp 190–191 °C (after recrystallization from ethanol). Anal. Calcd for $C_{28}H_{30}N_2O_6S$: C, 64.34; H, 5.80; N, 5.36. Found: C, 64.72; H, 6.06; N, 5.21.

(B) Methyl 1-Benzenesulfonylindole-2-acrylate and 1b. A mixture of 8.0 g of **1b** and 2.5 g of the acrylate was stirred at 100 ± 5 °C for 4 days. The material was chromatographed on silica gel with 1:1:1 ether–chloroform–hexane for elution. The product-containing fractions were combined and dissolved in a small amount of ether. The adduct **3b** crystallized in several successive crops: 2.95 g (73%); mp 162–165 °C (after recrystallization from methylene chloride–hexane).

Anal. Calcd for $C_{31}H_{28}N_2O_6S$: C, 66.89; H, 5.07; N, 5.03. Found: C, 66.72; H, 5.12; N, 5.01.

(C) Ethyl 1-Benzenesulfonylindole-2-acrylate and 1c. A mixture of **1c** (1.6 g) and the acrylate (350 mg) was heated to 105 °C for 2 days. The reaction mixture was chromatographed on silica by using 1:1:2 ether–hexane–chloroform. The product-containing fractions gave crystalline **3c** from ethyl acetate: 31% yield; mp 170–171 °C (after recrystallization from chloroform–hexane).

Anal. Calcd for $C_{28}H_{25}Cl_3N_2O_6S$: C, 52.99; H, 4.13; N, 4.58. Found: C, 52.77; H, 4.18; N, 4.53.

(D) Methyl 1-Benzenesulfonylindole-2-acrylate and 1c. A similar reaction of **1c** (32 g) with the methyl acrylate (7.7 g) was heated for 2 days at 100 °C. Chromatography using toluene–chloroform for elution gave **3d**: 1.7 g (13%); mp 212–214 °C (after recrystallization from chloroform–hexane).

Anal. Calcd for $C_{26}H_{23}Cl_3N_2O_6S$: C, 52.23; H, 3.88. Found: C, 51.46; H, 3.99.

Conversion of Carbamates 3a,b,d to 3e. Conversion of 3a to 3e. A solution of **3a** (24 mg) in acetonitrile (2.5 mL) was treated with *p*-toluenesulfonic acid (48 mg) and stirred overnight. Triethylamine (~0.5 mL) and methyl chloroformate (~0.25 mL) were added. After 15 min, ether was added and the ether solution washed with 2% hydrochloric acid and saturated sodium bicarbonate solutions. The solution was dried and evaporated to give crystalline **3e**, which was identical with a previously characterized sample.

Conversion of 3b to 3e. A solution of **3b** (50 mg) in CH_2Cl_2 (3 mL) at 0 °C was treated with trimethylsilyl iodide (50 mg) in 1 mL of CH_2Cl_2. After 30 min the solution was allowed to come to room temperature and treated with additional Me_3SiI (25 mg). After the mixture was stirred 1 h at room temperature, 1 mL of 0.3 N methanolic HCl was added. After 1 h the amine was isolated by an extractive workup, dissolved in ether, and treated with triethyl amine (0.2 mL) and methyl chloroformate (0.1 mL). After 0.5 h, product isolation gave **3e** (38 mg) identical with a previously characterized sample.

Conversion of 3d to 3e. A solution of **3d** (44 mg) in THF (1 mL) and 90% acetic acid (5 mL) was treated with zinc dust (150 mg) added in several portions over 1 h while the solution was kept at 0 °C. The zinc was filtered and washed with additional 90% acetic acid. The solution was then made basic and extracted with ether. The dried ether solution was treated with triethylamine (~0.50 mL) and methyl chloroformate (~0.25 mL). After 15 min the solution was washed and dried as above to give **3e** (32%) identical with a previously characterized sample.

Reactions of 3a,b,d with Potassium *tert*-Butoxide. (A) Conversion of 3a to 5a. A solution of **3a** (62 mg) in anhydrous THF (5 mL) was treated with potassium *tert*-butoxide (100 mg) and stirred 1 h at room temperature. The mixture was poured into ammonium chloride solution and extracted with ether. The product **5a** (57%) crystallized from ether–hexane and was identical with **5a** prepared as in part C below.

(B) Conversion of 3b to 5b. A solution of **3b** (350 mg) in anhydrous THF (25 mL) was treated with solid potassium *tert*-butoxide (250 mg). After being stirred for 20 min, the solution was poured into cold ammonium chloride solution and the product isolated by ether extraction. Recrystallization from methanol–water gave **5b**: mp 141–142 °C; 55% yield.

Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.09; H, 5.81; N, 6.73. Found: C, 72.14; H, 5.86; N, 6.70.

(C) Conversion of 3d to 5a. A solution of **3d** (250 mg) in dry THF (25 mL) was treated with solid potassium *tert*-butoxide (520 mg). After 2 h, the solution was worked up as for **3a**. The crude product was purified by elution through a small silica column by using 1:1:1 ether–chloroform–hexane to give **5a**: 127 mg (80%); mp 157–158 °C (after recrystallization from ether–hexane).

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.08; H, 6.87; N, 7.32. Found: C, 69.10; H, 6.87; N, 7.31.

Isolation of Intermediate 16 from Reaction of 3c with Potassium *tert*-Butoxide. A solution of **3c** (104 mg) was dissolved in anhydrous THF, and this solution was added to a solution of 210 mg of potassium *tert*-butoxide in 10 mL of dry THF. The mixture was stirred at room temperature for 5 min, immediately poured into aqueous ammonium chloride, and extracted with ether. Compound **16** (26% yield) was separated from some completely converted product (**5a**) by chromatography and recrystallized from ether–hexane; mp 150–152 °C.

Anal. Calcd for $C_{31}H_{30}N_2O_7SCl$: C, 60.72; H, 5.44. Found: C, 61.00; H, 5.60.

Reaction of 5a, 6a, 5f, 6f, and 7f with *p*-Toluenesulfonic Acid. Samples of **5f** and **6f** (3 mg each) were treated separately in acetonitrile (0.5 mL) with *p*-toluenesulfonic acid (3 mg). After 15 min the solutions were poured into aqueous sodium bicarbonate solution and extracted into chloroform. TLC showed approximately equivalent amounts of **5f** and **6f** in *each* sample. More extended reaction times lead to complete loss of TLC-mobile material. Analogous behavior was noted for **5a** and **6a**. Preparative-scale experiments with **5a** led only to uncharacterizable polar material which, however, clearly retained, from NMR data, unchanged *tert*-butoxy groups.

A reaction of **7f** (4 mg) with *p*-toluenesulfonic acid (8 mg) showed no change after 10 h at room temperature.

1-Benzenesulfonyl-6-nor-20-deethylcatharanthine (9) from 3a. A solution of **3a** (100 mg) in acetonitrile (20 mL) was treated at each of four 2-h intervals with 50 mg of *p*-toluenesulfonic acid over a total reaction time of 8 h. The resulting solution was then stirred overnight with a solution of formaldehyde (~100 mg) in tetrahydrofuran, prepared by passing a stream of gaseous formaldehyde generated by thermal depolymerization of paraformaldehyde through THF at −78 °C. The reaction mixture was poured into dilute HCl, extracted with ether, and basified. The product was extracted into methylene chloride and obtained in nearly quantitative yield as an amorphous glass after drying. Alternatively, a 55% yield was obtained when solid paraformaldehyde was added directly to the acetonitrile solution at the end of the deprotection, but this method was not totally reliable. The product obtained by either method showed NMR peaks from impurities at 1.30 and 1.85 ppm which are attributed to *tert*-butyl groups and acetyl groups, possibly introduced at the indole 3-position by electrophilic substitution during the deprotection step. These peaks dissappeared after purification by preparative layer chromatography (1:1 ethyl acetate–chloroform containing 1% methanol on alumina) to give pure **9** (60–70% yield) as a glass. The material was not obtained in crystalline form.

1-Benzenesulfonyl-6-nor-20-deethylcatharanthine (9) from 3b. A solution of **3b** (100 mg) in methylene chloride (10 mL) was cooled to 0 °C and treated with a solution of 75 mg of trimethylsilyl iodide in 1 mL of methylene chloride. After 30 min the ice bath was removed, and, after the mixture was stirred an additional 20 min at room temperature, an additional 50 mg of Me_3SiI was added in 0.5 mL of methylene chloride. After an additional 0.5 h at room temperature, there was added 2 mL of 0.3 N HCl in methanol. The solution was stirred 1 h at room temperature and then worked up by an extraction sequence to give the amine **8** as a glass. This was dissolved in acetonitrile (20 mL), and *p*-toluenesulfonic acid (100 mg) was added, followed by a solution of THF containing ~30 mg of formaldehyde. After the mixture was stirred 16 h at room temperature, an extractive workup gave **9**, 60 mg (80% yield). This material did not show the contamination characteristic of the preceding method.

6-Nor-20-deethylcatharanthine (10). A solution of **9** (50 mg) in methanol (20 mL) was treated successively at three 2-h intervals

with a total of 1500 mg of Na_2HPO_4 and 600 mg of 6% sodium amalgam. After a total 6-h reaction time the heterogeneous suspension was poured into water and the resulting solution decanted from the mercury. The solution was extracted with methylene chloride to give, after drying, **10** (29 mg, 85%) as a glass. Crystalline material was obtained from ether–hexane (mp 170–180 °C dec) and purified as the hydrochloride, mp 230 °C dec.

Anal. Calcd for $C_{18}H_{19}N_2O_2Cl \cdot 0.5H_2O$: C, 63.62; H, 5.93; N, 8.24. Found: C, 63.42; H, 5.95; N, 8.18.

1-Benzenesulfonyl-6-nor-15-methoxy-15,20-dihydro-20-deethylcatharanthine (11). A solution of **3a** (50 mg) in acetonitrile (10 mL) was treated with 50 mg of *p*-toluenesulfonic acid and stirred 2 h at room temperature. An additional 50 mg of *p*-toluenesulfonic acid was then added, and stirring was continued an additional 3 h. The reaction mixture was then diluted with 5% hydrochloric acid, washed with ether, basified, and extracted with methylene chloride to give **8**. The amine was dissolved in methanol (10 mL), and *p*-toluenesulfonic acid (25 mg) and formaldehyde (~40 mg in 5 mL of THF) were added. The solution was stirred 16 h at room temperature, and the product amine **11** (11 mg) was isolated by the usual extraction sequence and purified by preparative TLC on alumina with 50:50:1 ether–ethyl acetate–methanol.

Stability of 9 in Acidic Methanol. Stirring **9** (30 mg) with *p*-toluenesulfonic acid (50 mg) in methanol for 4 h returned **9** (28 mg) unchanged. Similarly, stirring for 16 h in acetonitrile (5 mL) containing methanol (0.5 mL) and *p*-toluenesulfonic acid (50 mg) gave a good recovery of **9** (23 mg).

6-Nor-15,20-dihydro-20-deethylcatharanthine (13). (A) From 5b by Reaction with Pd Black and Formic Acid Followed by Formaldehyde. To a solution of **5b** (50 mg) in methanol (10 mL) there were added Pd black (25 mg) and 5 mL of 10% formic acid in methanol. The solution was stirred at room temperature, and the Pd quickly became more flocculent in appearance. After 15 min the solution was poured into 2% HCl and extracted with ether., The aqueous layer was carefully basified and extracted with CH_2Cl_2. The extract was dried and evaporated and the residue dissolved in methanol (3 mL) containing acetic acid (0.2 mL) and 37% formalin solution (0.2 mL). This solution was kept overnight at room temperature. An extractive work up gave 35 mg (100%) of **13** which was further purified by preparative layer chromatography on alumina with 1:1 chloroform–ethyl acetate containing 1% methanol for elution. A crystalline sample was obtained from ether–hexane; mp 156–157 °C.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 72.71; H, 6.86; N, 9.41.

(B) From 5b by Reaction with Pd Black and Cyclohexadiene Followed by Formaldehyde. The debenzylation could also be carried out by using cyclohexadiene as the hydrogen source. **5b** (21 mg), cyclohexadiene (50 mg), and Pd black (25 mg) were stirred for 10 min, and the solution was filtered and treated with formalin (0.25 mL) and acetic acid (0.25 mL). After 2 h, extractive workup gave **13** (13 mg, 85%).

(C) From 3b via Reductive Desulfonylation of 15. A solution of **3b** (250 mg) in methanol (50 mL) was stirred under nitrogen and treated first with 1,4-cyclohexadiene (500 mg) and then, cautiously, with palladium black (70 mg). The solution was stirred 1 h, filtered, and then poured into 2% HCl. An extractive workup gave 175 mg of basic material which was dissolved in methanol (25 mL) and treated with formalin (0.5 mL) and acetic acid (0.5 mL). This solution was stirred overnight and processed by an extractive workup to give crude basic product (165 mg). Purification of preparative alumina plates gave 70 mg of pure noncrystalline **15** (35%). This material was dissolved in anhydrous methanol (25 mL) and treated three successive times at 2-h intervals with a total of 1800 mg of Na_2HPO_4 and 750 mg of 6% sodium amalgam. After a total reaction period of 6 h the mixture was poured into water, decanted from mercury, and extracted to give **13** [31 mg (65%); mp 156–157 °C] which was identical by spectral criteria with the previously isolated samples.

Reaction of 5b with Trimethylsilyl Iodide. A solution of **5b** (40 mg) in dry methylene chloride (10 mL) was treated at 0 °C with a solution of methylene chloride (1 mL) containing trimethylsilyl iodide. After 15 min the reaction was quenched by pouring the mixture into ice–water and extracting with methylene chloride. After the extract was washed with sodium bicarbonate solution, dried, and evaporated, 32 mg of a reddish glass showing a single TLC spot was obtained. The NMR spectrum indicated the retention of the benzyloxy group (two singlets at 5.0 ppm) and methoxy groups (singlets at 3.55 and 3.60 ppm) and indicated formation of two isomeric products. The vinyl protons which appears as two well-defined overlapping triplets in all the azabicyclooctenes appear as a broadened triplet at 6.8 ppm. This material was not further studied.

Reaction of 8 with Acetaldehyde. Amine **8** was prepared from **3a** (100 mg) under the usual conditions. Acetaldehyde (~100 mg) was added and the solution stirred at room temperature for 48 h. The reaction mixture was poured into dilute HCl and extracted with ether before being basified. The basic product was extracted with methylene chloride. The product (33 mg) was obtained as a glass after purification on a neutral alumina preparative TLC plate with 1:50:50 methanol–ethyl acetate–ether for development.

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Registry No. 1a, 79356-98-2; **1b**, 79328-85-1; **1c**, 66531-21-3; **1d**, 79328-86-2; (±)-**3a**, 79328-87-3; (±)-**3b**, 79328-88-4; (±)-**3c**, 79328-89-5; (±)-**3d**, 79328-90-8; (±)-**3e**, 79328-91-9; (±)-**4a**, 79328-92-0; (±)-**5a**, 79328-93-1; (±)-**5b**, 79328-94-2; (±)-**8**, 79328-95-3; (±)-**9**, 79328-96-4; (±)-**10**, 79328-97-5; (±)-**10**·HCl, 79328-98-6; (±)-**11**, 79328-99-7; (±)-**12**, 79329-00-3; (±)-**13**, 79329-01-4; (±)-**14**, 79329-02-5; (±)-**15**, 79329-03-6; (±)-**16**, 79329-04-7; (±)-**17**, 79329-05-8; pyridine, 110-86-1; phenyl chloroformate, 1885-14-9; 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine, 79329-06-9; methyl 1-benzenesulfonylindole-2-acrylate, 79329-07-0; ethyl 1-benzenesulfonylindole-2-acrylate, 79329-08-1.